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Paracetamol interaction with oral contraceptive steroids: increased plasma concentrations of ethinyloestradiol

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1 The effect of a single dose of paracetamol (1 g) on plasma concentrations of the oral contraceptive steroids ethinyloestradiol (EE_2) and levonorgestrel (LNG) has been studied in six healthy female volunteers.

2 The area under the plasma concentration-time curve (AUC_{0-24}) of EE_2 was significantly increased following paracetamol administration by 22% (control 2221 ± 291; following paracetamol, 2702 ± 452 pg ml^{-1} h; mean ± s.d.; $P \leqslant 0.05$). The greatest effect was evident in the time period 0–3 h. There was a significant decrease in the AUC of EE_2-sulphate after paracetamol (7736 ± 3791 pg ml^{-1} h) compared with control (13161 ± 4535 pg ml^{-1} h; $P \leqslant 0.05$).

3 Plasma concentrations of LNG were unaltered by concurrent paracetamol administration.

4 We conclude that the administration of a single 1 g dose of paracetamol causes an increase in plasma concentrations of EE_2 as a result of a reduction in the sulphation of the steroid. This interaction may be of clinical significance in women on oral contraceptive steroids who regularly take paracetamol.

Keywords paracetamol contraceptive steroids interaction

Introduction

Paracetamol is metabolised primarily by conjugation with sulphate and glucuronic acid when given in therapeutic doses *in vivo*, but some microsomal oxidation leading to the formation of cysteine and mercapturate conjugates also occurs (Prescott, 1980). Since both glucuronidation and sulphation are capacity-limited, there are dose-dependent changes in the pattern of urinary conjugates *in vivo* (Clements *et al.*, 1984). In addition, a single dose of paracetamol (1.5 g) has been shown to cause partial depletion of inorganic sulphate in man (Levy *et al.*, 1982; Morris & Levy, 1983; Hendrix-Treacy *et al.*, 1986). These findings are clearly of significance when considering the concurrent administration of other drugs metabolised by sulphoconjugation and interactions of paracetamol have been reported with salicylamide (Levy & Yamada, 1971) and with the dopaminergic agonist fenoldopam (Ziemniak *et al.*, 1985).

The oral contraceptive steroid ethinyloestradiol (EE_2) is extensively conjugated with sulphate and this occurs to a greater extent in the gut mucosa than the liver (Back *et al.*, 1982). We have previously shown in an *in vitro* model that the presence of paracetamol reduces the sulphation of EE_2 in the gastrointestinal mucosa (Rogers *et al.*, 1987). The aim of the present work was to examine the effect of a conventional single dose of paracetamol (1 g) on plasma concentrations of EE_2 in the 24 h period following ingestion of an oral contraceptive preparation.

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Methods

Subjects

The subjects studied were six healthy females (aged 21–24 years) who had been using a combined oral contraceptive preparation for at least 3 months. They were taking no other drugs. The study was approved by the Mersey Regional Hospital Ethics Committee and the nature of the study explained to each subject.

Experimental design

Following an overnight fast each subject received a single oral dose of Ovran (EE_2 50 μg; LNG 250 μg) in place of their normal OC preparation. The study was performed in the second half of the menstrual cycle. At approximately the same time in a subsequent cycle the study was repeated but this time a single dose of paracetamol (2 × 0.5 g tablets) was administered 1 h before the OC. Blood samples (10 ml) were obtained from an indwelling forearm cannula at 0, 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 11, 14 and 24 h. Plasma was separated by centrifugation (2000 rev min^{-1} for 10 min) and stored at −20° C.

Steroid assays

Plasma EE_2 and LNG were measured by radioimmunoassay (Back *et al.*, 1979; 1981a). For analysis of EE_2-sulphate the following procedure was adopted: Plasma samples (100–200 μl) were incubated with sulphatase enzyme (*Helix pomatia* preparation, Type H1; 30 units in acetate buffer, pH 5.0, 200 μl) for 3 h at 37° C. Since the enzyme preparation also hydrolyses β-glucuronides, glucurolactone (3.6 mg; 150 μl in acetate buffer) was included. The incubation procedure was terminated by the addition of diethyl ether (3 ml). The extracted EE_2 was measured by radioimmunoassay. EE_2-sulphate concentrations were calculated by subtracting the previously found values of unconjugated EE_2. In three patients, sufficient plasma was available to determine concentrations of EE_2-glucuronide; this was done by omitting the glucurolactone from the incubation.

Pharmacokinetic analysis

The area under the plasma concentration-time curve (AUC) was calculated for EE_2 for the periods 0–3, 0–6, 0–11 and 0–24 h by the trapezoidal rule by means of a Hewlett Packard programmable calculator. $AUCs_{0-24}$ were calculated for LNG, EE_2-sulphate and EE_2-glucuronide.

Statistical analysis was by Student's paired *t*-test.

Results

The effect of pre-dosing with paracetamol (1 g) on the EE_2 plasma concentration profile is shown in Figure 1. There was a significant difference ($P \leq 0.05$) in AUC when calculated for each of the time periods 0–3, 0–6, 0–11 and 0–24 h (Table 1). However, it is evident from the percentage increase in AUC that the greatest effect is seen in the early time periods. Between 0–3 h a 54% increase (control, 602 ± 114; + paracetamol, 926 ± 252 pg ml^{-1} h) was seen but for the period 0–24 h the increase was 22% (control, 2221 ± 291; + paracetamol, 2702 ± 452 pg ml^{-1} h). There was a significant decrease in the AUC_{0-24} of EE_2-sulphate (Table 2; Figure 3) following paracetamol administration (control, 13.2 ± 4.5; + paracetamol, 7.7 ± 3.8 ng ml^{-1} h).

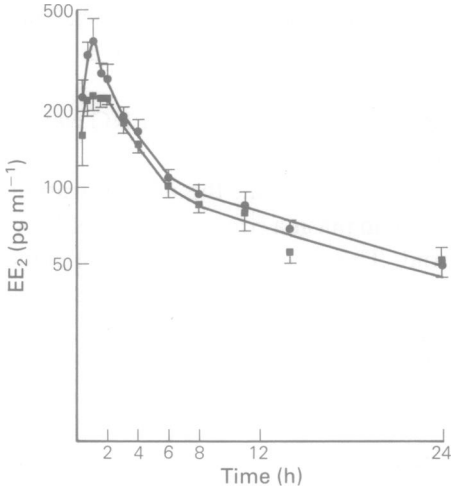

Figure 1 Plasma concentrations of ethinyloestradiol (EE_2) following oral administration of 50 μg (+ 250 μg levonorgestrel). ■, control; ●, 1 h after a single oral dose of paracetamol (1 g). Data are presented as mean ± s.d. ($n = 6$).

Table 1 Effect of a single dose of paracetamol (1 g) on the area under the curve (AUC) obtained for EE_2 for the time periods 0–3, 0–6, 0–11 and 0–24 h

Time (h)	*Control*	*AUC (pg ml^{-1} h) + paracetamol*	*% increase*
0–3	602 ± 114	*926 ± 252	54
0–6	1010 ± 153	*1417 ± 265	40
0–11	1442 ± 166	*1897 ± 320	32
0–24	2221 ± 291	*2702 ± 452	22

Results are mean ± s.d. of six subjects.
*$P < 0.05$; significantly different from control.

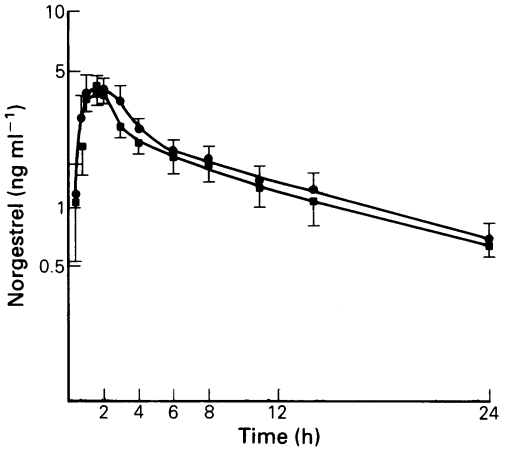

Figure 2 Plasma concentrations of levonorgestrel (LNG) following oral administration of 250 μg (+ 50 μg EE_2). ■, control; ●, 1 h after a single oral dose of paracetamol (1 g). Data are presented as mean ± s.d. (n = 6).

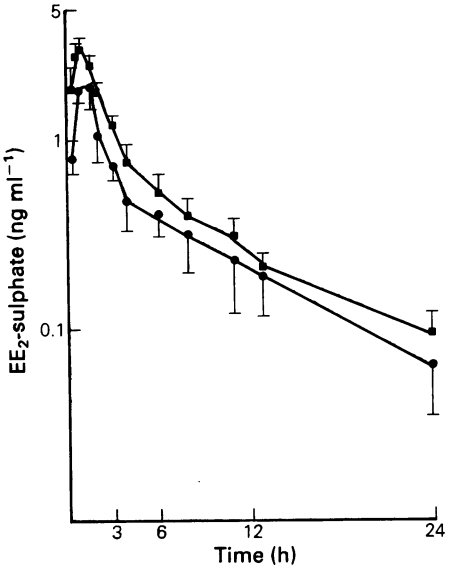

Figure 3 Plasma concentrations of ethinyloestradiol sulphate (EE_2-sulphate) following oral administration of 50 μg EE_2 (+ 250 μg LNG). ■, control; ●, 1 h after a single oral dose of paracetamol (1 g). Data are presented as mean ± s.d. (n = 6).

In the three subjects in whom sufficient plasma was available to assay for EE_2-glucuronide there was a trend towards an increase in plasma concentrations following paracetamol (Table 2). There was no effect of paracetamol on LNG plasma concentrations (Figure 2; Table 2; control, 35.3 ± 12.3; + paracetamol, 39.5 ± 13.7 ng ml^{-1} h).

Table 2 Effect of a single dose of paracetamol (1 g) on the area under the curve (AUC) obtained for LNG, EE_2-sulphate and EE_2-glucuronide for the time period 0–24 h

	AUC_{0-24} (ng ml^{-1} h)	
	Control	*+ paracetamol*
LNG	35.3 ± 12.3	39.5 ± 13.7
EE_2-sulphate	13.2 ± 4.5	7.7 ± 3.8*
EE_2-glucuronide†	8.3 ± 4.5	16.2 ± 1.8

Results are mean ± s.d. of six subjects except † where data are from three subjects.
*$P < 0.05$; significantly different from controls.

Discussion

The main finding of this study is that the overall systemic availability of EE_2 is increased following oral administration if paracetamol is given concurrently. The decrease in plasma concentrations of EE_2-sulphate is consistent with paracetamol competing for the sulphation mechanism with the oral contraceptive. Since the major part of the first pass metabolism of EE_2 occurs in the gut mucosa (Back *et al.*, 1982) and also a previous *in vitro* study has shown paracetamol to reduce EE_2-sulphation in the mucosa (Rogers *et al.*, 1987), the intestine rather than the liver is probably the primary site of the interaction.

Clearly, competition for available sulphate in the gut mucosa is only applicable to drugs which undergo sulphation at this site. Previously, ascorbic acid (vitamin C) has been shown to impair EE_2-sulphation in women, leading to increased plasma concentrations of EE_2 (Back *et al.*, 1981b). This interaction is considered to take place in the gut mucosa (i.e. a localized depletion of endogenous sulphate) since up to 6 g of ascorbic acid fails to deplete systemic sulphate concentrations (Morris & Levy, 1983). Although paracetamol does not undergo pronounced first pass metabolism (Clements *et al.*, 1984), *in vitro* findings point to a small percentage of the drug being conjugated in the mucosa (Rogers *et al.*, 1987). Given the massive differences in dose of paracetamol (1000 mg) and EE_2 (50 μg), the sulphation of a few percent of paracetamol could be significant to either cause localized depletion of sulphate or saturation of ATP-sulphurylase (Rogers *et al.*, 1987).

However, competition for available co-substrate in the gut wall may only account for a part of the inhibitory effect of paracetamol on

EE_2-sulphation. Paracetamol is mainly metabolized in the liver to both sulphate and glucuronic acid conjugates. The effect of paracetamol on body stores of endogenous sulphate has been studied by Morris & Levy (1983) who showed a decrease of 24%, 2 h after a dose of 1.5 g paracetamol. Likewise, Hendrix-Treacy *et al.* (1986) demonstrated that a 650 mg dose resulted in a temporary partial depletion of plasma sulphate which was most marked at 2 h and returned to control values at 6 h.

It is therefore evident from the foregoing discussion that a single oral dose of paracetamol (1 g) given to the volunteers in the present study should have significantly depleted serum sulphate levels and thus both hepatic and intestinal PAPS stores. The largest increase in the AUC of EE_2 occurred in the time period 0–3 h (Table 1). This is consistent with the inorganic sulphate concentrations reaching a nadir 2–3 h after paracetamol ingestion (Levy *et al.*, 1982; Hendrix-Treacy *et al.*, 1986).

An interesting observation in the present study was that the reduction in EE_2-sulphation appeared to be partially compensated by an increase in the formation of EE_2-glucuronide. Unfortunately a lack of plasma in three subjects did not allow a more definite assessment of this. Increased glucuronidation as a compensatory mechanism for reduced sulphation *in vivo* has been described for a number of drugs including paracetamol (Galinsky & Levy, 1981; Clements *et al.*, 1984) and salicylamide (Levy & Matsuzawa, 1967; Caldwell *et al.*, 1982). Houston & Levy (1976) also reported that a decrease in excretion of paracetamol sulphate caused by ascorbic acid administration was balanced by a corresponding increase in the glucuronic acid conjugate.

We conclude that administration of single dose paracetamol (1 g), 1 h prior to an oral contraceptive causes an increase in plasma concentrations of EE_2 as a result of a reduction in the sulphation of the steroid. No effect was observed on plasma concentrations of levonorgestrel since this steroid undergoes extensive reduction prior to conjugation. This interaction may be of clinical significance in women on oral contraceptive steroids who regularly take paracetamol and who will consequently have higher EE_2 concentrations than are required for contraceptive purposes.

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